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Factors Influencing Adherence to GLP-1 Receptor Agonist Therapy Among Patients Receiving Weight-Loss Injections

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have revolutionized the management of obesity and type 2 diabetes mellitus, with clinical trials demonstrating weight reductions exceeding 15% and significant cardiovascular benefits. However, a substantial and persistent gap exists between the efficacy observed in randomized controlled trials and the real-world effectiveness of these therapies, primarily driven by poor patient adherence and high discontinuation rates. This review synthesizes current evidence on the multifactorial determinants of GLP-1 RA adherence among patients using these medications for weight loss. Drawing upon real-world data from North America, Europe, Latin America, and Asia, we examine the physiological, psychological, economic, and healthcare system-related barriers that undermine treatment persistence. Gastrointestinal adverse effects, particularly nausea and vomiting, represent the most frequently cited physiological barrier, with discontinuation rates peaking during dose escalation. Economic barriers, including high out-of-pocket costs and inconsistent insurance coverage, profoundly impact adherence, with persistence falling below 10% in unsubsidized settings. Psychological factors, including the transient suppression of appetitive drive and the resurgence of "food noise" upon missed doses, further complicate long-term adherence. Healthcare system factors, including the quality of patient-provider communication, the provision of comprehensive education about dose titration and expected outcomes, and the availability of integrated nutritional and behavioral support, emerge as critical modifiable determinants of treatment persistence. This review proposes an integrated care framework incorporating medical nutrition therapy, structured lifestyle support, and patient-centered communication strategies to bridge the efficacy-effectiveness gap and optimize clinical outcomes in patients receiving GLP-1 RA therapy for weight management.

Keywords: GLP-1 receptor agonists; treatment adherence; medication persistence; obesity management; weight-loss injections; gastrointestinal tolerability; healthcare costs; patient education.

Introduction

1. Introduction and Background

1.1 The Therapeutic Revolution of GLP-1 Receptor Agonists

The therapeutic landscape for obesity and type 2 diabetes mellitus (T2DM) has been fundamentally transformed by the advent of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) [1]. These innovative medications enhance glucose-dependent insulin secretion, suppress pancreatic glucagon production, slow gastric motility, and reduce body weight by increasing satiety and decreasing appetite [2]. From the initial introduction of short-acting agents to the current dominance of long-acting analogues—including semaglutide, liraglutide, dulaglutide, and the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RA tirzepatide—these pharmacotherapies have substantially expanded the non-surgical treatment options available for obesity and cardiometabolic disease [3]. Randomized controlled trials (RCTs) have consistently demonstrated efficacy profiles previously unattainable with non-surgical interventions. Foundational studies such as STEP and SURPASS established high benchmarks for weight reduction, with recent data from the SURMOUNT-5 head-to-head trial demonstrating that dual agonism with tirzepatide can achieve mean body weight reductions exceeding 20% [4]. Furthermore, landmark trials such as SELECT have confirmed significant reductions in major adverse cardiovascular events (MACE), establishing these agents as systemic disease-modifying therapies beyond glycemic and weight control [5]. Recent guidelines from the American Diabetes Association recommend that GLP-1 RAs should be considered when atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease predominates, independent of glycated hemoglobin (A1C) levels [6].

1.2 The Persistence Gap: Efficacy Versus Real-World Effectiveness

Despite these demonstrated benefits, a critical dichotomy has emerged between the highly supervised environment of RCTs and the realities of routine clinical practice [7]. While RCTs report

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retention rates often exceeding 85% over 68 weeks, real-world evidence from diverse healthcare systems consistently indicates that a substantial proportion of patients discontinue therapy within the first year [8]. This attrition fundamentally undermines the chronic disease management model required for obesity and diabetes care, leading to weight regain, metabolic rebound, and the forfeiture of long-term cardiovascular protection. The magnitude of this persistence gap varies considerably across regions and patient populations. In the United States, a study of 4,066 commercially insured obese adults without diabetes who initiated GLP-1 therapy found that only 32.3% remained persistent at one year, with adherence rates (proportion of days covered ≥80%) of just 27.2% [9]. Similarly, a large-scale IQVIA analysis revealed that 15% of all approved GLP-1 prescriptions are abandoned at the pharmacy counter without a single fill, while an additional 36% of patients discontinue therapy immediately following their first fill [10]. In obesity-focused or high out-of-pocket-cost settings such as Poland and Colombia, persistence falls below 10% at 12 months, with some cohorts showing persistence below 15% by 24 months [11]. This persistence gap is not merely a statistical curiosity; it has profound clinical and economic implications. Individuals who persist with GLP-1 RA therapy achieve significant A1C reductions, are more likely to achieve an A1C of <7%, and experience fewer hospitalizations and shorter hospital stays [12]. The financial implications are equally staggering: by early 2025, GLP-1 costs accounted for approximately 15% of the entire commercial pharmacy benefit expenditure in the United States, reaching $29.15 per member per month, with much of this expenditure yielding limited clinical benefit due to early discontinuation [9].

1.3 Rationale and Scope of This Review

Understanding the factors that influence adherence to GLP-1 RA therapy is essential for developing effective strategies to bridge the efficacy-effectiveness gap. While previous research has provided initial insights regarding various reasons for discontinuation, the contributors to therapy persistence have not been well defined or comprehensively synthesized [13]. This review aims to provide a systematic analysis of the multifactorial determinants of GLP-1 RA adherence among patients receiving these medications for weight loss, drawing upon real-world evidence from diverse healthcare systems and integrating physiological, psychological, economic, and healthcare system perspectives.

2. Defining and Measuring Adherence and Persistence

2.1 Conceptual Framework

A clear distinction between adherence and persistence is essential for understanding the factors influencing GLP-1 RA therapy continuation. The World Health Organization defines adherence to long-term therapy as "the extent to which a person's behavior—taking medication, following a diet and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider" [14]. Adherence thus refers to conformity with dosing recommendations, encompassing both the timing and dosage of medication administration. Persistence, in contrast, refers to the continuity of therapy over time—the duration from treatment initiation to discontinuation [15]. These constructs are measured using distinct methodologies in real-world studies. Adherence is commonly assessed using the proportion of days covered (PDC) or medication possession ratio (MPR), with a threshold of ≥80% typically considered adherent [15]. Persistence is typically measured as the absence of a gap in therapy exceeding a specified threshold (commonly 60 or 90 days) [9]. It is important to note that these definitions are not standardized across studies, with allowable gap thresholds ranging from 60 to 90 days and some studies measure persistence as a binary outcome at a fixed time horizon while others measure it as a continuous variable [11].

2.2 Methodological Challenges in Adherence Research

Several methodological challenges complicate the interpretation of adherence and persistence data in GLP-1 RA research. First, real-world datasets are subject to potential biases related to insurance coverage, healthcare system structure, and reimbursement policy, which vary markedly across regions [11]. Second, operational definitions of persistence and discontinuation differ substantially across sources, precluding direct quantitative comparison of persistence percentages across cohorts [9]. Third, claims-based measures of adherence may not fully capture patients' actual medication-taking behavior at home, as prescription refill patterns represent indirect measures of medication use [16]. Despite these limitations, the consistency of findings across diverse healthcare systems and study designs provides compelling evidence for the existence of a substantial persistence gap and points toward common underlying drivers.

3. Global Epidemiology of GLP-1 RA Adherence and Persistence

3.1 North America

In the United States, the uptake of GLP-1 RAs has increased rapidly, yet persistence rates remain markedly low. The market is characterized by high out-of-pocket costs, complex insurance utilization management, and recurrent supply shortages [11]. A comprehensive analysis of 4,066 commercially insured obese adults without diabetes who initiated GLP-1 therapy in 2021 found that overall GLP-1 persistence was 46.3% at 180 days and 32.3% at one year [9]. Adherence rates were equally concerning, with a mean one-year PDC of 51.0% and only 27.2% of patients achieving a PDC ≥80%. Persistence varied significantly among GLP-1

products, with once-weekly injectable semaglutide (Ozempic) demonstrating the highest median persistence at 279 days, followed by once-weekly dulaglutide (Trulicity) at 230 days. Daily injectable liraglutide products (Saxenda and Victoza) had the lowest median persistence at approximately 120 days [9]. These findings are consistent with the broader literature demonstrating that reduced dosing frequency is associated with improved adherence [17].

3.2 Europe

European data, derived largely from national registries, provide insight into adherence patterns within systems with stricter prescribing indications and varying reimbursement structures. In Sweden, where GLP-1 RA therapy for T2DM is covered within the public reimbursement framework, a study of 73,895 new users reported a cumulative discontinuation incidence of 23.6% at one year and 38.5% at three years—corresponding to one-year persistence of approximately 76.4% [18]. Notably, among patients who discontinued, 41.1% reinitiated therapy within one year, suggesting that discontinuation in the Swedish context is frequently transient rather than terminal. Danish nationwide register data provide the largest and most methodologically detailed European reference point. Analyzing 44,343 first-time GLP-1 RA users with T2DM, Lassen et al. reported a 12-month discontinuation risk of 21.2% (corresponding to 12-month persistence of 78.8%) [19]. However, only 48.6% of patients met the adherence threshold of PDC ≥0.80 at 12 months—indicating that a substantial proportion of patients formally remain on therapy but are intermittently adherent. A marked socioeconomic gradient was also documented: the 12-month discontinuation risk was 24.5% in the lowest household-income tertile compared with 18.0% in the highest, even within a publicly reimbursed system with a capped annual co-payment [19]. In contrast, data from Poland illustrate the pronounced incremental impact of unsubsidized medication costs. An analysis of the Polish LUX MED database found that only 6.6% of patients achieved long-term use (defined as ≥12 consecutive prescriptions), with 35.1% receiving only a single prescription [20]. The absence of state reimbursement for obesity pharmacotherapy, combined with prohibitive out-of-pocket costs, resulted in a 12-month persistence of only 6.6% [20].

3.3 Latin America

Data from Latin America reveal profound disparities in access and persistence driven by socioeconomic barriers. A 2025 retrospective study of 9,356 new semaglutide users in Colombia documented a rapid decline in the persistence curve: 35.4% abandoned treatment after a single month, with a mean duration of use of only 93.7 days. By six months, persistence had fallen to 13.8%, and at 12 months, only 0.2% of the cohort remained on therapy [21]. This steep decline demonstrates that, without subsidized healthcare infrastructure and integrated clinical follow-up, the therapeutic potential of GLP-1 RAs is largely negated by economic realities.

3.4 Asia and the Middle East

Data from Asia and the Middle East reveal unique adherence patterns influenced by metabolic phenotypes and healthcare access. Evidence from a Saudi tertiary-care cohort indicates that, although GLP-1 RAs are widely prescribed, 12-month persistence with injectable semaglutide is lower than with oral sodium-glucose cotransporter 2 inhibitors (approximately 40% versus a higher rate with SGLT2 inhibitors), suggesting that injection burden and cost may drive patients toward oral alternatives [22]. It has been hypothesized that East Asian populations may experience a higher incidence of gastrointestinal adverse events with fixed-dose GLP-1 RA therapy because of lower average body surface area relative to non-East Asian populations, though this proposition requires further investigation [23].

4. Physiological Barriers to Adherence

4.1 Gastrointestinal Adverse Events

Gastrointestinal (GI) adverse events remain the most frequently cited medical reason for discontinuation across both clinical trial and real-world settings [24]. The mechanisms underlying these events are intrinsically linked to GLP-1 pharmacology: GLP-1 inhibits gastric emptying and reduces bowel motility through a vagally mediated gastric braking mechanism, prolonging the sensation of fullness while simultaneously driving upper GI symptoms [25]. In the largest cross-sectional survey of GLP-1 RA discontinuation in routine practice, surveyed patients most frequently cited nausea (64.4%) and vomiting (45.4%) as their principal reasons for abandoning treatment [26]. A qualitative study of 36 adults with T2DM found that among discontinuers (n=20), the most commonly identified challenges leading to treatment discontinuation were side effects (55%) and high cost (50%) [13]. Similarly, a recent cross-sectional study of 91 non-persistent GLP-1 RA users found that adverse effects were the primary reason for stopping in 52% of participants, followed by medication shortages (33%) and cost (25%) [27]. Importantly, discontinuation rates peak during the dose-escalation phase. As higher-dose formulations are developed to maximize weight-loss outcomes, the physiological burden intensifies. The 2025 STEP UP trial, which evaluated an investigational 7.2 mg dose of semaglutide, found that GI adverse events occurred in approximately 71% of participants in the high-dose group, compared with 61% receiving the standard 2.4 mg dose and 43% receiving placebo [28]. This dose-dependent increase in toxicity suggests that aggressive titration without concurrent strategies to optimize gastric volume management and meal composition

substantially increases the risk of early patient discontinuation.

4.2 Dietary Modulation of Gastrointestinal Tolerability

The interaction between dietary composition and GLP-1 pharmacology is central to tolerability. Dietary lipids are potent stimulators of endogenous gut hormones, including cholecystokinin and peptide YY, which act synergistically with GLP-1 to inhibit gastric emptying [29]. When a patient receiving a high-dose GLP-1 RA consumes a high-fat meal, the combined effect of pharmacological and endogenous lipid-mediated signaling can produce profound gastric stasis, resulting in prolonged retention of gastric contents, fermentation, distension, and stimulation of mechanoreceptors that trigger the emetic reflex [30]. Nutritional strategies to mitigate GI symptoms include transitioning from three large meals to five or six smaller, nutrient-dense feedings to reduce mechanical distension of the stomach; reducing fat load per meal to attenuate postprandial nausea; and ensuring adequate hydration to prevent constipation and mitigate the secondary reduction in fluid intake due to suppressed thirst perception [30]. During acute nausea episodes, particularly during dose escalation, the transition to liquid or semi-solid foods may facilitate gastric transit [11].

4.3 Lean Mass Loss and Sarcopenia Risk

The rapid weight loss induced by high-dose GLP-1 RAs is accompanied by substantial reductions in fat-free mass, which may impair muscle function and predispose to clinical sarcopenia, particularly in older adults and those with baseline sarcopenic obesity [31]. Reduction in fat-free mass during weight loss is not equivalent to sarcopenia, which is a clinical syndrome defined by reduced muscle strength or physical performance in addition to low muscle mass. Nevertheless, preserving fat-free mass during pharmacologically induced weight loss remains a clinically important goal. The standard population-level Recommended Dietary Allowance (0.8 g/kg/day) was derived from nitrogen-balance studies in healthy younger adults underweight-maintenance conditions and is insufficient for patients in a substantial catabolic state, in older adults, or in those with chronic disease [32]. The PROT-AGE international position paper recommends a minimum daily intake of 1.0–1.2 g/kg/day for healthy older adults and 1.2–1.5 g/kg/day for those with acute or chronic illness [33]. In the specific context of intentional weight loss, protein intakes at the upper end of this range (≥1.2 g/kg/day and up to approximately 1.6 g/kg/day), combined with resistance exercise, are recommended to attenuate the disproportionate loss of fat-free mass that otherwise accompanies negative energy balance [34].

5. Psychological Barriers to Adherence

5.1 Appetitive Drive and "Food Noise"

A critical psychological driver of both early treatment success and subsequent relapse is the modulation of appetitive drive, commonly described in patient-reported accounts as "food noise"—a colloquial construct describing maladaptive prospection and cue-driven mental simulation of short-term food rewards [35]. GLP-1 receptors are densely expressed in the hypothalamus (arcuate nucleus) and the hindbrain (area postrema and nucleus of the solitary tract), where their activation enhances satiety signaling and attenuates the hedonic drive for food [36]. Recent neuroimaging and behavioral studies indicate that GLP-1 RAs also suppress activity within the mesolimbic reward circuitry and modulate the default mode network, effectively reducing maladaptive food-related prospection [37]. However, the suppression of appetitive drive appears to be transient and incomplete. A pivotal case study using an advanced brain-computer interface to continuously monitor a patient with obesity and binge eating disorder undergoing tirzepatide therapy revealed that, while the dual agonist effectively suppressed signaling within the mesolimbic reward circuitry, this suppression was transient [37]. These findings suggest that GLP-1 therapies may not permanently remodel the deep neural architecture governing impulse control, meaning the pharmacological dampening of the reward pathway could be largely reversible [38].

5.2 The Rebound Effect and Weight Regain

The abrupt resurgence of intrusive food-related cognitions upon a missed dose or discontinuation can be profoundly distressing, frequently precipitating rapid weight regain and a sense of treatment failure [39]. A meta-analysis examining the consequences of GLP-1 RA discontinuation found that patients typically regain a substantial proportion of the weight lost during treatment, with the rate and magnitude of regain depending on the duration of therapy and the intensity of concomitant lifestyle interventions [40]. This pattern of weight regain has important implications for adherence motivation. Patients who perceive their weight loss as contingent upon continued medication use may be more motivated to persist with therapy, whereas those who experience significant weight regain following missed doses may become discouraged and discontinue treatment entirely. The cyclical pattern of initiation, discontinuation, and reinitiation—observed in approximately 41% of Swedish patients who discontinued GLP-1 RA therapy—suggests that many patients cycle in and out of treatment, potentially reflecting struggles with both the physiological and psychological challenges of long-term therapy [18].

5.3 Treatment Satisfaction and Perceived Efficacy

Perceived treatment efficacy is a well-established predictor of medication adherence across chronic conditions [41]. In the context of GLP-1 RA therapy, patients who perceive tangible benefits—including weight loss, improved glycemic control,

and enhanced well-being—are more likely to persist with treatment. A qualitative study of 36 adults with T2DM found that among continuers (n=16), the most commonly identified facilitators supporting the decision to continue were observations of improved glucose control (50%) and weight loss (55%) [13]. Conversely, lack of perceived efficacy is a significant driver of discontinuation. In the same study, 25% of discontinuers reported that "numbers did not improve" as their primary reason for discontinuation [13]. This pattern is consistent with the broader literature on medication adherence, which emphasizes the importance of the interplay between perceived necessity (the perceived value of a medication) and perceived concerns (the sense of burden associated with it) [42]. Treatment satisfaction, which encompasses both perceived efficacy and tolerability, is also an important determinant of adherence. Studies with GLP-1 RAs have demonstrated that less frequent dosage administration is associated with greater treatment satisfaction and improved quality of life, outcomes that may lead to increased adherence [17].

6. Economic and Structural Barriers to Adherence

6.1 Cost as a Primary Barrier

The acquisition cost of GLP-1 RA therapy, and the distribution of that cost between patient out-of-pocket expense and payer coverage, is among the strongest determinants of treatment persistence globally. Manufacturer list prices in the United States substantially exceed those in other high-income countries: for semaglutide indicated for obesity (Wegovy 2.4 mg), the monthly U.S. list price of approximately $1,349 is approximately four-fold higher than in Germany ($328) and the Netherlands ($296) [43]. A peer-reviewed analysis of estimated minimum production costs suggested that semaglutide could be supplied at approximately $40 per 30-day course, indicating that current national prices primarily reflect manufacturer pricing strategy and patent protection rather than cost-of-goods constraints [44]. In the United States, out-of-pocket costs and utilization management function as direct barriers to persistence. A dose-response relationship exists between cost-sharing and adherence: patients in the highest out-of-pocket cost quartiles have significantly greater odds of nonadherence [45]. A recent microsimulation analysis demonstrated that, at current U.S. net prices, tirzepatide and semaglutide for obesity have lifetime incremental cost-effectiveness ratios of approximately $197,000 and $468,000 per quality-adjusted life-year, respectively—values that would require substantial price discounts to reach conventional cost-effectiveness thresholds [46].

6.2 Insurance Coverage and Formulary Restrictions

Insurance coverage policies profoundly impact access to and persistence with GLP-1 RA therapy. In the United States, coverage for GLP-1 RAs varies substantially by indication: while coverage for diabetes is standard, coverage for obesity is variable, with some patients facing high out-of-pocket costs or no coverage for these medications [47]. Medicare's current policy, which excludes anti-obesity medications unless prescribed for another condition like diabetes, exacerbates this issue [48]. This coverage gap not only fuels abandonment but also limits reinitiation, further weakening long-term adherence. Even when therapy is initiated, mid-year formulary changes or alterations in employer-sponsored coverage can interrupt therapy regardless of patient or physician preference [49]. A factor unique to the U.S. market is forced discontinuation resulting from such changes, which can occur multiple times over the course of a patient's treatment journey.

6.3 Global Variations in Reimbursement and Access

European reimbursement landscapes are highly heterogeneous, producing markedly different patterns of access and persistence within a single continent. The United Kingdom restricts National Health Service coverage of semaglutide for obesity to specialist weight-management services under NICE Technology Appraisal TA875 [50]. Germany has limited reimbursement following statutory assessment. Several Nordic countries provide partial coverage with patient co-payment, whereas Poland excludes obesity pharmacotherapy from public reimbursement entirely [11]. The continuity of the cost-persistence association across very different reimbursement environments is instructive. Even within the Danish universal healthcare system, where reimbursable medication is covered at 100% beyond a fixed annual co-payment of approximately $630, Lassen et al. demonstrated a 36% higher relative risk of 12-month discontinuation in the lowest household-income tertile compared with the highest [19]. Together with the Sweden-Poland contrast and the international list-price disparities, these data indicate that GLP-1 RA persistence is driven not by reimbursement status as a binary variable but by the cumulative financial burden borne by the individual patient—a gradient that operates within reimbursed systems and intensifies dramatically in unsubsidized ones.

7. Clinical and Patient-Related Factors

7.1 Dosing Frequency and Formulation

Dosing frequency is a critical determinant of adherence to GLP-1 RA therapy. A substantial body of data supports a relationship between reduced dosing frequency and improved adherence. In a retrospective analysis using claim data from 3,623 patients with T2DM, once-daily liraglutide was associated with significantly better adherence than twice-daily exenatide, with an odds ratio for poor adherence (MPR <80%) of 1.33 (95% CI 1.16–1.53)

for exenatide versus liraglutide [51]. More recently, a large retrospective cohort study using claim data from >22,000 patients found that patients were significantly more likely to achieve an adherence rate of ≥80% if treated with once-weekly exenatide than with more frequently administered GLP-1 RAs [52]. The convenience of once-weekly versus once-daily administration is associated with better adherence in real-world studies involving this agent [17]. In a propensity-score matched analysis comparing dulaglutide with once-weekly exenatide and once-daily liraglutide, adherence (PDC ≥80%) at six months was 54% with dulaglutide compared with 38% with once-weekly exenatide and 44% with liraglutide [53]. The proportion of patients who discontinued treatment within the six-month follow-up was also significantly lower with dulaglutide than with once-weekly exenatide (26% vs. 48%) or liraglutide (28% vs. 36%) [53].

7.2 Delivery Device and Injection-Related Factors

Advances in dosage formulation and delivery devices may also increase adherence to GLP-1 RA therapy. Important differences exist in reconstitution and preparation procedures prior to administration for the various GLP-1 RAs. Dulaglutide single-dose prefilled pens come with the active drug already in solution and are ready to use without the need for mixing, whereas other once-weekly agents require reconstitution and preparation [17]. The availability of dulaglutide as a ready-to-use drug in solution reflects formulation and bioengineering advances designed to overcome the issue of reconstitution. Development of a device with a hidden, ready-attached needle (dulaglutide) may be helpful for patients with a fear of needles. In a 4-week trial of 211 injection-naive patients with T2DM evaluating the dulaglutide single-dose pen, the final injection-success rate was 99.1%, and >96% of patients reported that the device was easy to use, they were satisfied with the device, and they would be willing to continue its use after the study. Most patients favored not having to attach, touch, or see the needle (99%, 98.6%, and 95.7%, respectively) [54].

7.3 Patient-Provider Communication and Education

The quality of communication between patients and their healthcare providers is a critical modifiable determinant of GLP-1 RA adherence. A qualitative study comparing continuers and discontinuers found that continuers were more likely than discontinuers to receive clinically relevant information from their healthcare team, including facts about GLP-1 RA medications, likely treatment benefits, the importance of gradual dose titration, and the need to adjust diet after initiation [13]. Specifically, 93.8% of continuers (vs. 75% of discontinuers) confirmed receiving information about GLP-1 RA medications and having their questions answered when starting therapy. Importantly, only 50% of discontinuers versus 75% of continuers confirmed receiving information about the importance of gradual dosage titration [13]. This finding suggests that continuers may have been more likely than discontinuers to be started on a "low-dose" regimen at the time of initiation, which could account for the higher percentage of continuers versus discontinuers who reported "minimal or no side effects" with treatment (87.5% vs. 55.0%, respectively). Continuers were also more likely than discontinuers (62.5% vs. 40%) to receive proactive phone contacts from their healthcare team during the first few months so that any concerns could be addressed [13]. Through these interactions, participants likely received feedback on their progress, making them more aware of any tangible benefits that might be accruing. These findings highlight the importance of thorough patient education and ongoing support in promoting treatment persistence.

7.4 Therapeutic Inertia

Therapeutic inertia—the failure of healthcare providers to initiate or intensify therapy when indicated—represents a significant barrier to optimal glycemic control and may indirectly affect adherence by undermining patient confidence in treatment effectiveness [55]. In a real-world study of 7,392 adults with T2DM, therapeutic inertia was observed in 38.0% of the study population [55]. Among individuals who were suboptimally controlled (HbA1c ≥7.5%) and receiving GLP-1 RA therapy, 88.9% received treatment intensification during follow-up, whereas among non-GLP-1 RA users, only half received intensified therapy [55].

8. Strategies to Improve Adherence

8.1 Medical Nutrition Therapy and Lifestyle Support

The integration of Medical Nutrition Therapy (MNT) and structured lifestyle support represents a physiologically plausible and clinically necessary framework to narrow the persistence gap [11]. In a position paper published in late 2025, the Academy of Nutrition and Dietetics stated that all individuals receiving obesity pharmacotherapy should have concurrent access to evidence-based MNT delivered by a registered dietitian nutritionist [30]. The integration of MNT extends beyond symptom management and may confer pharmacoeconomic value. In the most closely related population—adults with dyslipidemia and cardiometabolic risk factors—a systematic review and meta-analysis of multiple individual MNT sessions delivered by registered dietitian nutritionists demonstrated clinically meaningful improvements in lipids, glycemia, body mass index, and blood pressure, together with reduced need for lipid-lowering medications and net cost savings primarily driven by reduced medication use [56]. Key nutritional strategies to support GLP-1 RA therapy include transitioning from three large meals to five or

six smaller, nutrient-dense feedings; reducing fat load per meal; ensuring adequate hydration; and using liquid or semi-solid foods during acute nausea episodes [30]. Implementing protein targets of 1.2–1.6 g/kg/day of adjusted or ideal body weight, distributed across three to four daily meals, combined with resistance training two to three times weekly [32]. Screening for iron, vitamin B12, vitamin D, and calcium status, with routine supplementation as indicated [30].

8.2 Behavioral and Digital Interventions

Behavioral interventions target the psychological barriers and habit-formation processes critical for long-term persistence. The most successful weight-loss trials to date have incorporated intensive lifestyle interventions as a core component of the trial protocol, modeled on the structured behavioral curricula pioneered by the Diabetes Prevention Program [57]. In these trials, the comparator arm typically received the same lifestyle intervention without active GLP-1 RA therapy, indicating that the GLP-1 RA effect is additive to, rather than independent of, structured behavioral support. Given the global shortage of specialized dietitians and behavioral therapists, digital platforms have been proposed as a scalable strategy for delivering structured behavioral support. Company-published real-world data from the Omada Health Enhanced GLP-1 Care Track, analyzing 1,124 self-enrolled commercially insured adults without diabetes, reported retention rates of 94% at 12 weeks and 84% at 24 weeks, with mean weight loss of 12.1% among members who persisted through the 24-week program compared with 7.4% among those who discontinued early [58]. While these outcomes substantially exceed published real-world persistence estimates, the underlying cohort is self-selected, digitally engaged, and predominantly commercially insured, which limits direct comparability with broader real-world populations. In a separately designed randomized controlled trial, Mathioudakis et al. compared a fully autonomous artificial intelligence-driven lifestyle intervention application against traditional human coaching within a digital Diabetes Prevention Program framework. The AI-driven intervention was statistically noninferior to human-led coaching for weight loss and glycated hemoglobin reduction and outperformed human coaching on engagement metrics, with higher rates of program initiation (93.4% vs. 82.7%) and overall completion (63.9% vs. 50.3%) [59].

8.3 Reframing Therapeutic Goals

A critical strategy for improving patient persistence is reframing the therapeutic objective from weight loss alone to cardiovascular risk reduction. The SELECT trial demonstrated a 20% reduction in MACE among patients with obesity and established cardiovascular disease [60]. A prespecified sub-analysis suggested that the cardiovascular benefit was not fully explained by the magnitude of total weight loss achieved: reductions in waist circumference mediated only approximately one-third of the treatment effect [61]. These data indicate that GLP-1 RAs function as direct vascular and systemic disease-modifying agents, operating through anti-inflammatory pathways and endothelial stabilization, rather than solely through adiposity reduction [62]. From a clinical counseling perspective, this distinction is of considerable importance. Educating patients that the medication confers cardiovascular and cerebrovascular protection independently of the magnitude of weight loss may provide the necessary motivation to maintain adherence through inevitable weight-loss plateaus.

8.4 Policy and Systemic Interventions

Systemic changes are necessary to fully realize the potential of GLP-1 therapies. Payers and health systems should incentivize and reimburse the support services that promote medication persistence, recognizing that the considerable cost of these agents is largely forfeited if patients discontinue therapy within the first year [11]. Addressing the coverage gap for obesity pharmacotherapy—particularly in Medicare and other publicly funded programs—would reduce financial barriers to access and persistence. Additionally, the pharmacological pipeline is evolving to address adherence barriers directly. Recently approved or emerging daily oral small-molecule GLP-1 agonists may improve access and reduce injection burden [63]. The development of ultra-long-acting formulations and the exploration of dose de-escalation protocols—examining whether patients can sustain metabolic benefits on lower maintenance doses combined with intensive lifestyle interventions—represent promising avenues for future research.

9. Conclusion

The global evidence consistently demonstrates that, while GLP-1 RAs are highly effective agents for weight loss and metabolic improvement, their real-world impact is substantially diminished by poor long-term persistence. The attrition of patients—driven by gastrointestinal intolerance, prohibitive costs, psychological challenges, and insufficient behavioral support infrastructure—represents a significant inefficiency in healthcare delivery. Narrowing this persistence gap will require a shift from a prescription-centered model to an integrated care approach. Consistent with the December 2025 World Health Organization guidelines, obesity should be managed as a chronic, relapsing disease in which pharmacotherapy is explicitly paired with evidence-based dietary guidance and structured lifestyle support [64]. Medical Nutrition Therapy should be systematically offered as a standard component of care rather than an optional adjunct, applied proactively to mitigate side effects and reduce the risk of sarcopenia. Protein

intake should be prescribed with individualized targets and monitored with the same rigor applied to glycated hemoglobin. Scalable behavioral health interventions, including AI-driven digital therapeutics, should be integrated to maintain therapeutic continuity between clinic visits. Equally important, the therapeutic objective should be reframed from weight reduction alone to comprehensive cardiovascular risk reduction and long-term health gain. The pharmacological pipeline is also evolving to address adherence barriers directly. Recently approved or emerging daily oral small-molecule GLP-1 agonists may improve access and reduce injection burden. Concurrently, other combination trials testing agents to preserve lean mass during weight reduction represent a vital avenue for actively addressing the metabolic consequences of pharmacologically induced weight loss [65]. In summary, while the pharmacology of metabolic disease management has advanced considerably, the care delivery systems required to support long-term treatment retention remain underdeveloped. The next decade must prioritize the construction of nutritional and behavioral infrastructure capable of supporting these therapies and closing the persistence gap. By bridging the disciplines of pharmacotherapy, nutritional science, and behavioral medicine, healthcare systems can optimize clinical and patient-centered outcomes in the GLP-1 era.

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